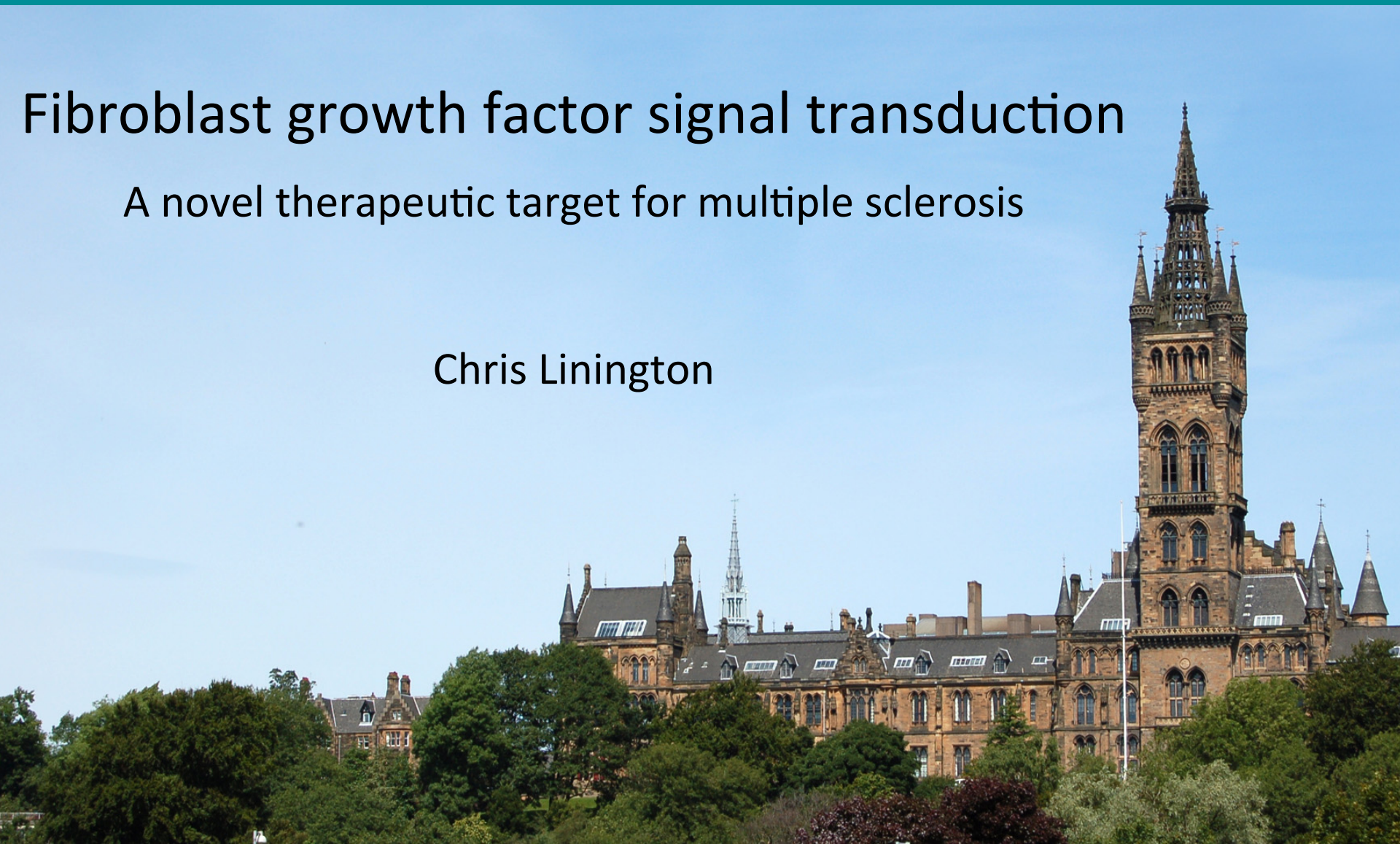
University of Glasgow | Institute of Infection, Immunity & Inflammation

Fibroblast growth factor signal transduction

A novel therapeutic target for multiple sclerosis

Chris Linington



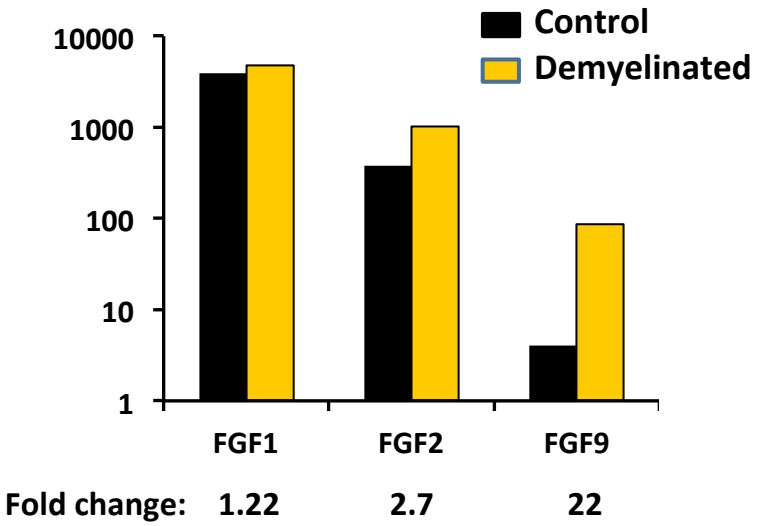
Developing an effective treatment for multiple sclerosis

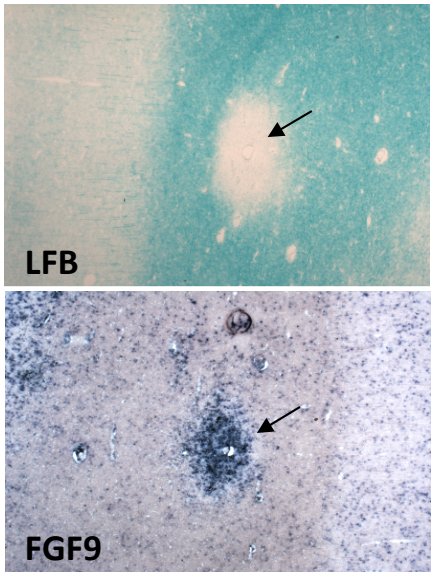
Dogma:	Chronic inflammatory demyelinating disease driven by a T cell dependent adaptive response originating in the periphery
Reality:	Current treatments suppress T cell mediated inflammation in brain but not halt accumulation of disability (Alezumimab, Tysabri)
Why:	Disability due to axonal injury/loss caused by inflammatory demyelinating response sequestered in central nervous system
Hypothesis:	This inflammatory activity is maintained by T cell independent responses originating within the CNS itself

Strategy – requires getting away from established models and returning to patients

- Identify candidates - analysis of MS lesions/CSF/serum
- Mechanistic studies *in vitro*
- Validate *in vivo* – develop new models
- Phase 1 clinical trials – repurposing existing drugs

FGF9 expression is up regulated in MS lesions

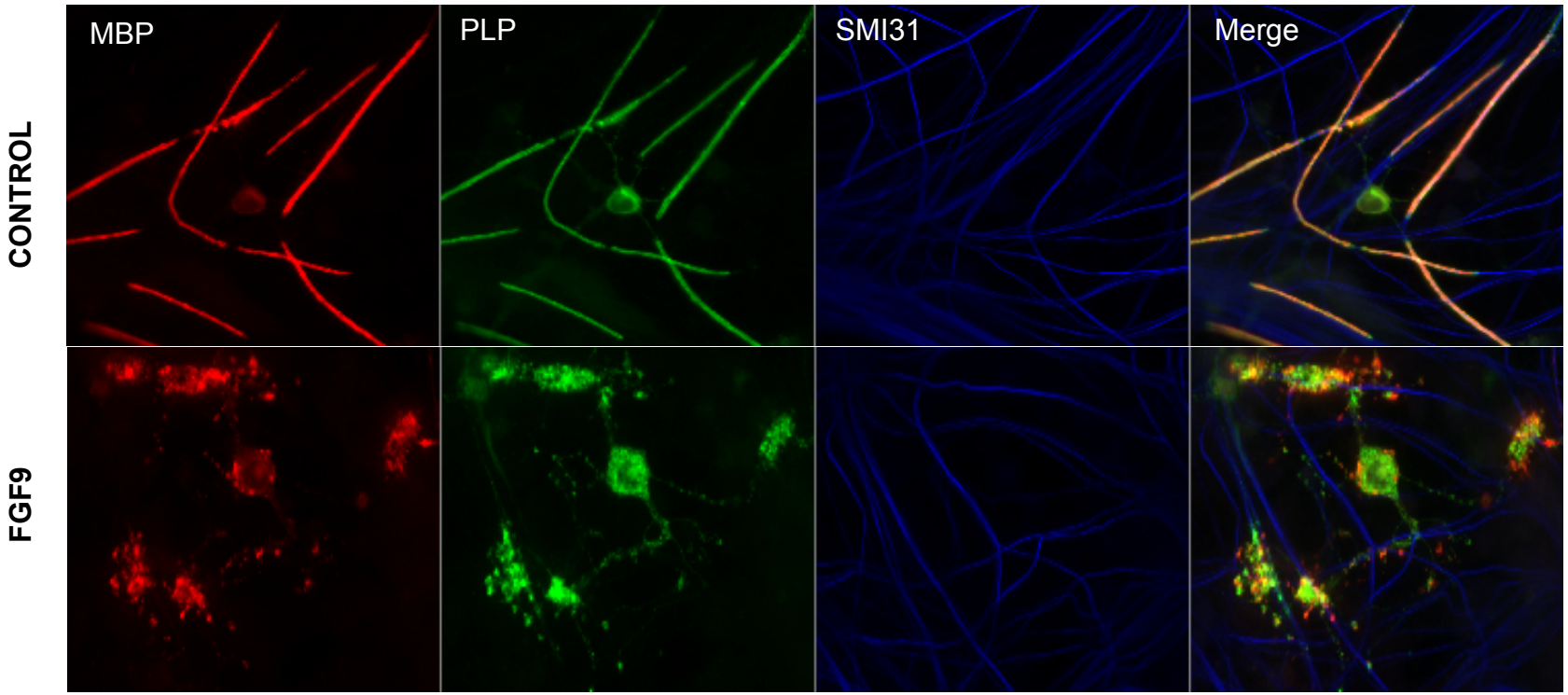




FGF9 Immunohistochemistry

Control white matter	negative
Active lesions	+++
NAWM	+
Glial scar tissue	negative

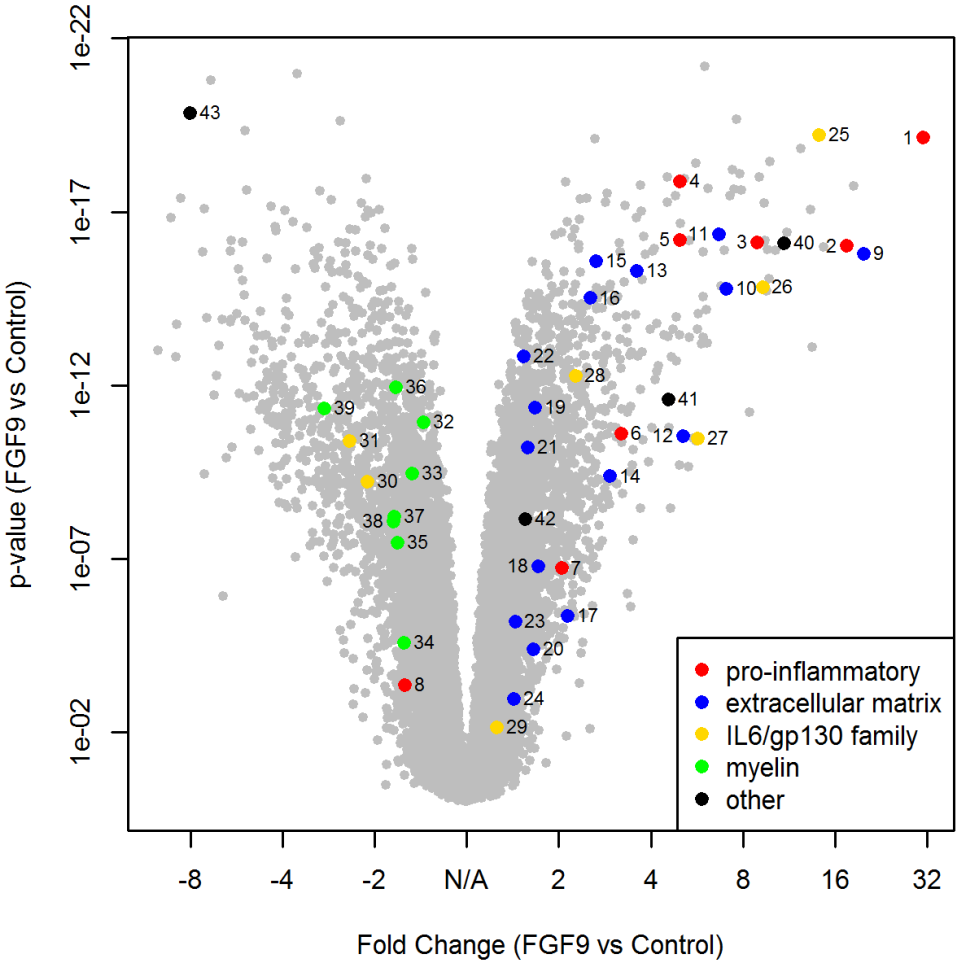
FGF9 inhibits (re)myelination in vitro



- Oligodendrocyte cell bodies swollen
- Accumulation of MBP & PLP immunoreactivity
- Formation of membranous extensions

Images acquired after ten days exposure (100ng/ml; DIV 18 to 28)

Inhibition of myelination is associated with a pro-inflammatory signature



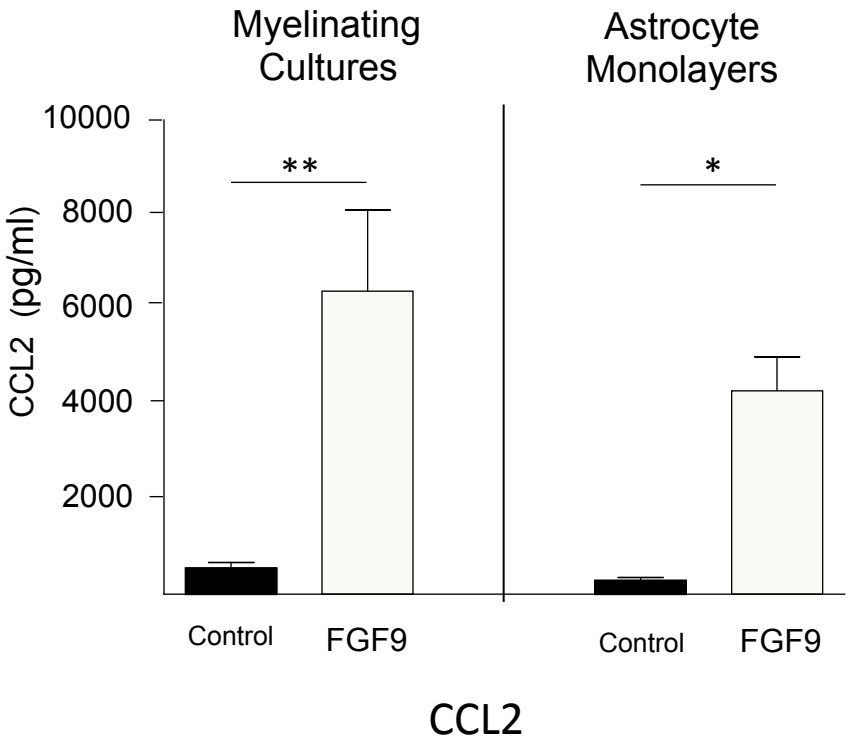
1752 transcripts up regulated

1510 transcripts down regulated

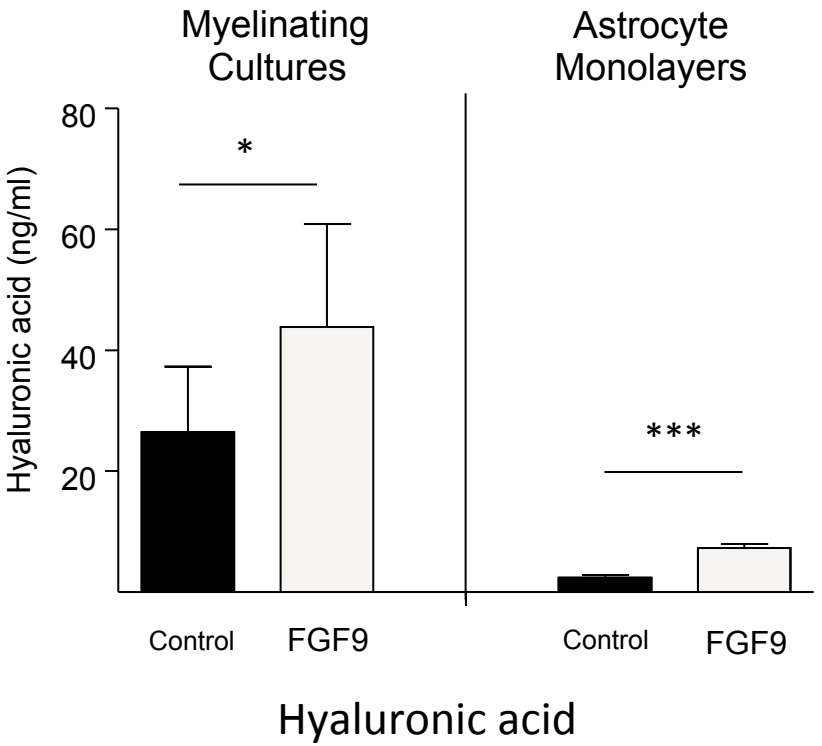
24 hours

Inflammatory		Extracellular matrix		Myelin	
1	ccl7	9	adamts1	32	plp1
2	cd93	10	itga5	33	cnp
3	cd63	11	igfbp3	34	opalin
4	il1rap	12	has2	35	mog
5	ccl2	13	chst3	36	omg
6	tnfrsf10b	14	adamts9	37	mbp
7	il1r1	15	cd44	38	mag
8	cxcl12	16	timp1	39	mobp
IL6/gp130 family		17	fn1		
25	clcf1	18	lama5	**Others**	
26	il11	19	mmp15	40	hbegf
27	lif	20	mmp3	41	vgf
28	osmr	21	itgb1	42	fgf2
29	il6	22	itgb8	43	hgf
30	stat2	23	icam1		
31	cntf	24	mmp11		

Induction of CCL2 is predominantly astrocytic



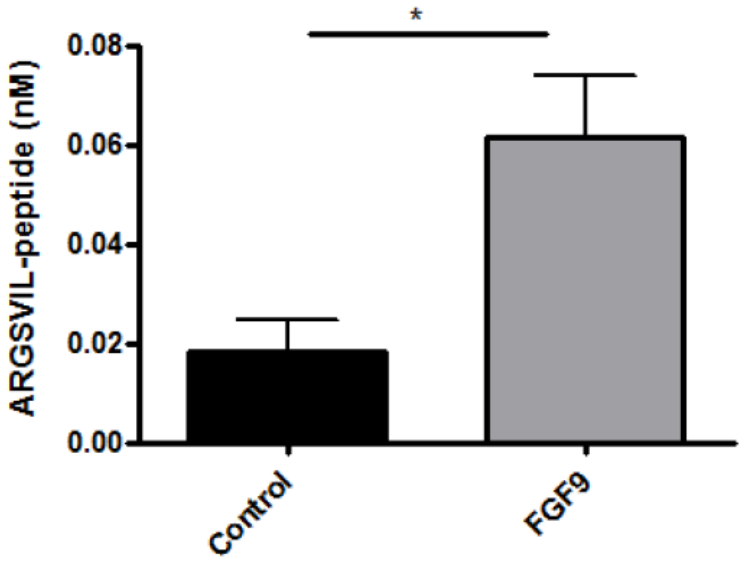
CCL2

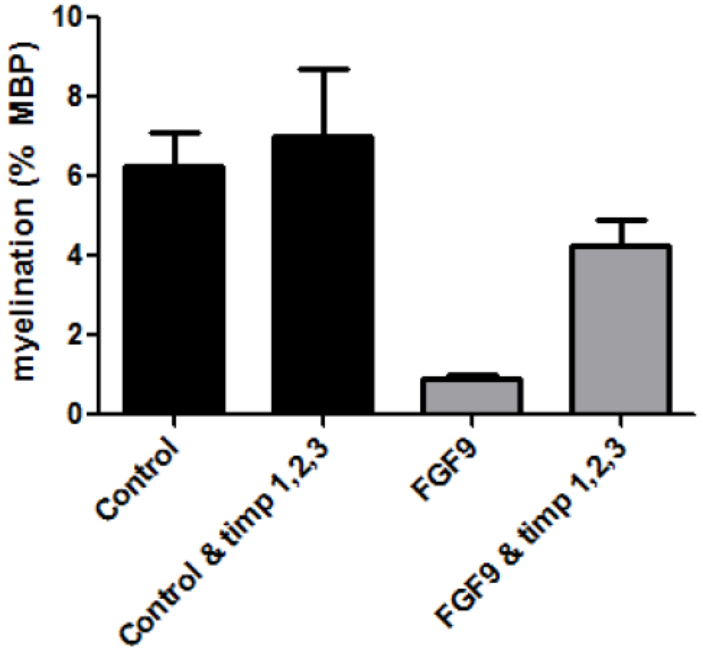


Hyaluronic acid

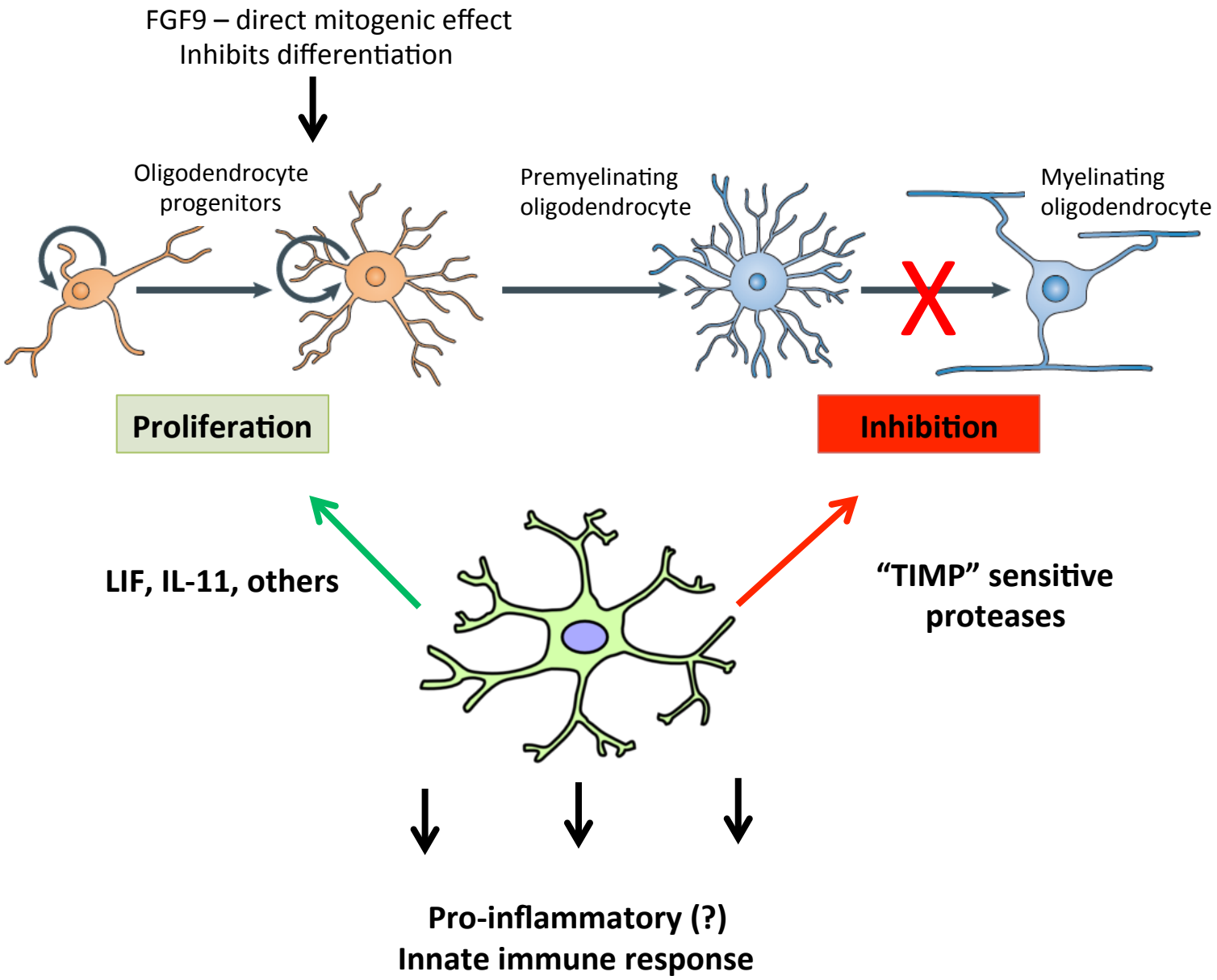
HA, hyaluronic acid – surrogate marker for increased activity of hyaluronic acid synthase 2 (*Has2* Fold Change > 4)

Induction of TIMP sensitive proteases contribute to inhibition of myelination by FGF9





FGF9 initiates a multifactorial astrocyte-dependent response



What happens in vivo?

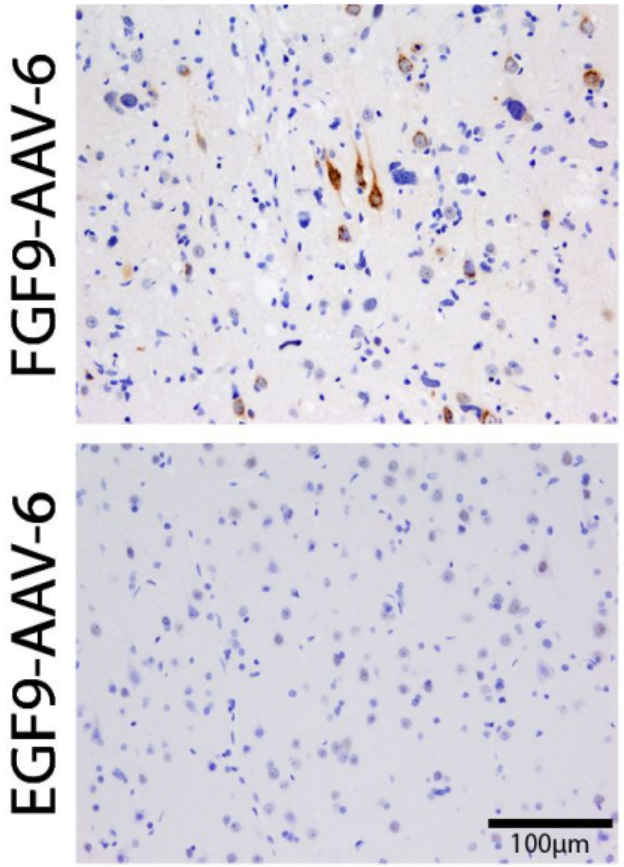
- As yet we have no EAE variant that reproduces disease associated changes in FGF9 expression observed in patients
- Binds to the extracellular matrix, short range effect, not detected in CSF

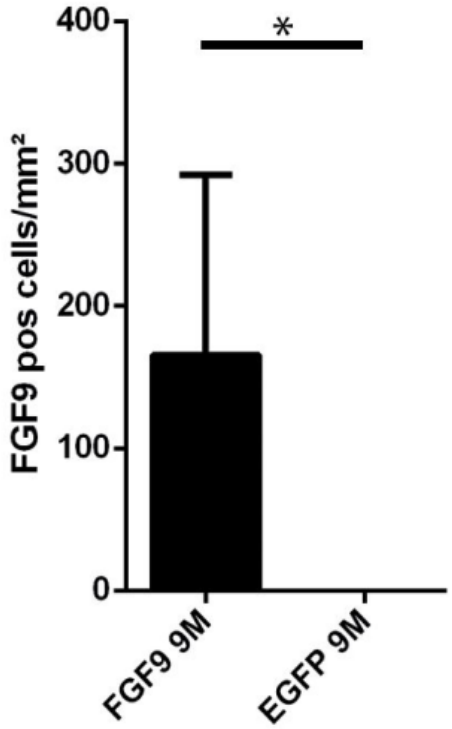
Inject adeno-associated viral vectors encoding FGF9 or EGFP
to induce persistent focal expression
in astrocytes

Analyse from 10 days till up to 9 months

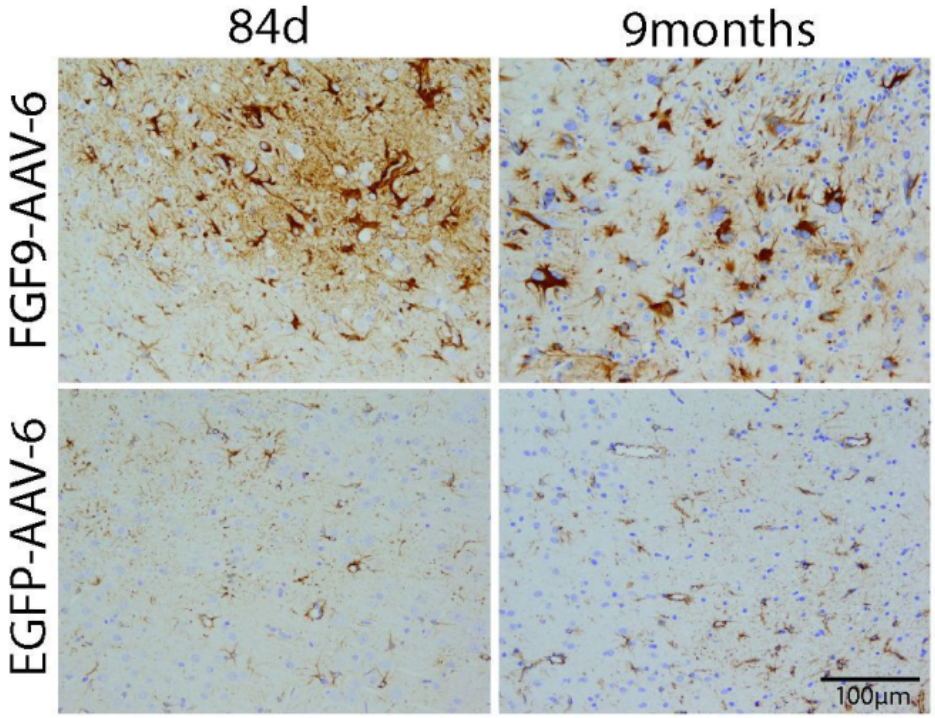
Christine Stadelmann, Claudia Wrzos, Göttingen

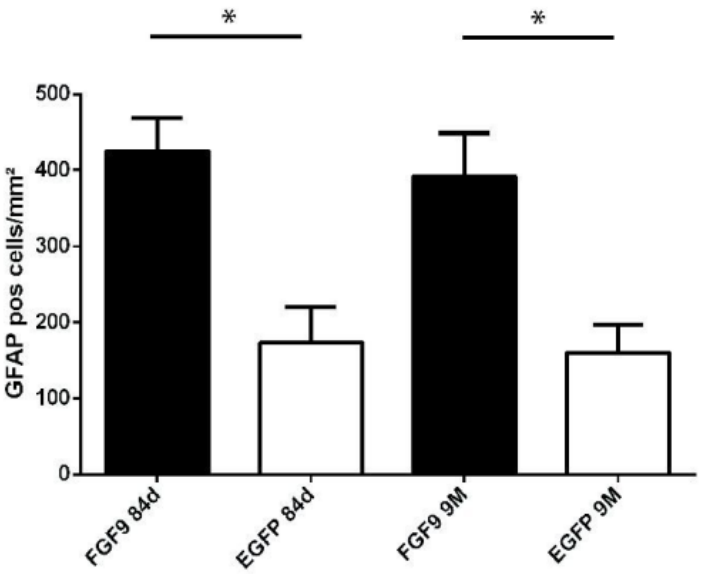
FGF9 expression is retained for at least 9 months



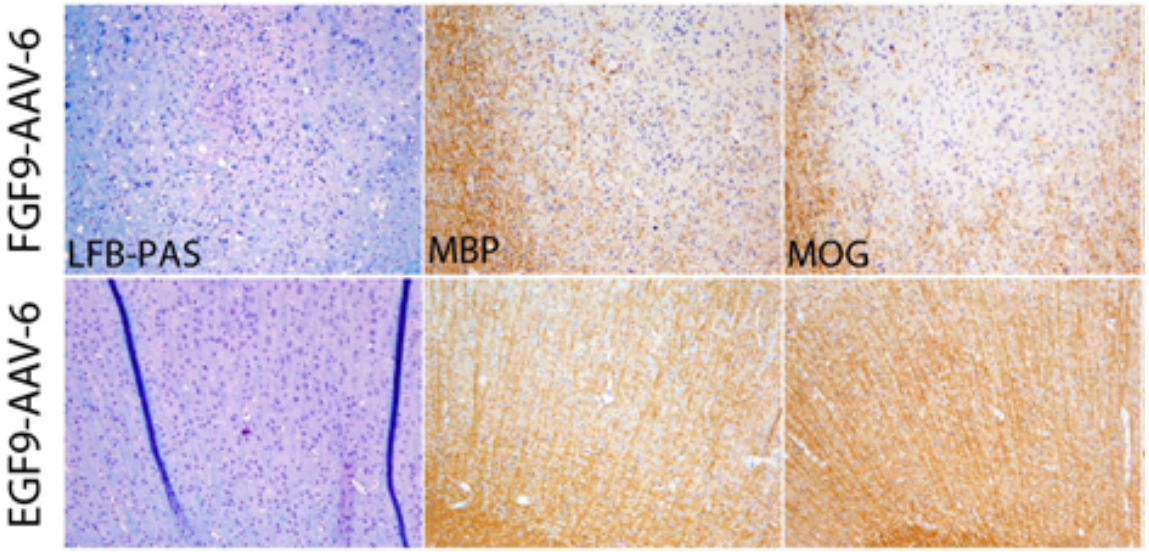


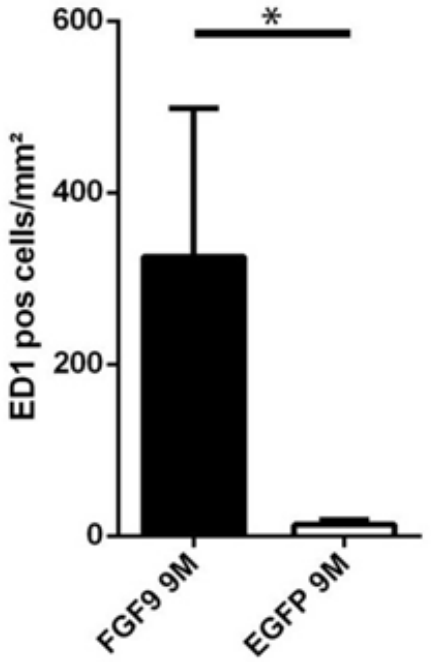
AAV-FGF9 induces a persistent astrocytic response





AVV-FGF9 induces “inflammatory” demyelination





Myelin loss/pallor observed at lesion site 30 days post-injection and becomes progressively more pronounced over time.

Summary

- FGF9 expression increased in MS tissues
  Active lesions > NAWM >> control white matter > glial scar

- In vitro FGF9 inhibits (re)myelination, stimulates OPC proliferation
  modulates multiple functional pathways

- In vivo persistent glial expression of FGF9 induces demyelination and inflammation in the adult rat CNS

- FGF9 mediated signal transduction – a novel therapeutic target to suppress disease progression in MS?

The unknowns:

- Why induced in MS lesions? Hypoxia?

- At what point are the effects of FGF9 still reversible?

- What is the best therapeutic strategy – selective FGFR inhibitors?

Acknowledgements

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